Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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Re: Docket Number 2005D-0330, Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods

Dear Docket Officer,

In Septemeber 2005, the FDA published a draft guidance entitled, Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods. BloodCenter of Wisconsin would like to take this opportunity to provide our comments on that document.

BloodCenter of Wisconsin is an independent blood center headquartered in Milwaukee, Wisconsin. We are the sole provider of blood and blood products to over 50 hospitals in Wisconsin, effectively touching the lives of nearly 60% of the state's population.

Our issues are discussed in detail in the following pages.

We are concerned that the requirements proposed in this draft guidance will substantially decrease the availability of apheresis platelets and push the industry to return to the manufacture of whole blood derived platelets; with the associated increase in donor exposure and the use of inferior bacterial detection methodologies.

Thank you for the opportunity to comment on this draft guidance.

Yours truly,

Jerome L. Gottschall

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Section III: Donor Selection and Management

The Draft Guidance states that prior to the first platelet donation the Platelets, Pheresis donors should be tested for WBC count and platelet count and these lab values be acceptable under the manufacturer's directions for use (Page 5, Section III A). There are currently no requirements for donor WBC count prior to or after apheresis collection in any regulation or by any manufacturer of automated blood cell separators. There is also no established acceptable range of donor WBC for collection of apheresis platelets. Compliance would be difficult or nearly impossible under our current collection setting and computer system. We do not believe that a WBC count would provide any benefit to the donor or patient.

Recommendation: Delete the requirement for WBC counts.

The Draft Guidance states that if you cannot test the donor before the first donation (i.e. at a mobile collection site) evaluate the donor's platelet and WBC counts after the first collection (Page 5, Section III A). Further details regarding this evaluation are needed. Is the FDA suggesting immediate post-donation samples be obtained or will post-collection evaluation of samples taken prior to the beginning of the collection suffice? We are of the opinion that post-donation samples would give a falsely low platelet count and be of no value regarding donor safety.

Recommendation: If one cannot test the donor before the first donation, samples should be collected pre-donation and then evaluated. Delete the requirement for WBC counts.

The Draft Guidance establishes more stringent deferral requirements for those donors who have ingested aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) than is currently used. For those donors who have taken ASA or ASA-containing drugs deferral of 5 days from the last dose and those who have taken NSAIDs deferral of 3 days from the last dose is recommended. (Page 5, Section III A) We are of the opinion that both of these deferral criteria are excessive. Although you referenced Patrono et al. (Chest 2001 supplement 119(1):39-63S) for the ASA deferral, we do not know of any data that support this criteria, particularly deferring donors longer than 3 days. In fact, your ASA deferral criteria conflicts with the AABB standards which states "defer for 36 hours after ingestion of aspirin" (5.4.1A, page 62, 23rd edition). In addition, from the in-vitro studies by Zeiler et al. (Transfusion 2004;44:1300-1305) ASA may not have the negative effect on platelet function and clinical effectiveness as previously thought. Zeiler et al. demonstrated no significant difference in platelet aggregation or other markers of platelet structural integrity or metabolic state on day 3 and 5 of apheresis platelets collected from donors who had taken 500mg ASA 12 hours prior to collection versus apheresis platelets collected from the same donors who had taken no medication prior to donation.

We question the use of ASPBO Donor Deferral Criteria: Drugs and Medication Impact on Blood Donor Eligbility (revised June 23, 2004) as a reference for the NSAIDs deferral criteria. This web-based deferral list of drugs is not a peer-review publication and lacks appropriate references. This drug deferral list is for ASPBO use and not considered industry standard. Furthermore, unlike ASA, the other NSAIDs have a short half-life and reversibly inhibit platelet cycloxygenase. Thus, deferral for 3 days after ingestion of

NSAIDs would seem to be unnecessary and could have a negative impact on apheresis platelet collection and availability.

Recommendation: Specific donor deferral requirements for the ingestion of aspirin or other drugs that affect platelet function, as currently stated, be deleted from the Guidance. In lieu, we recommend that the Guidance require that the collection facility establish a policy for the deferral of donors who have ingested drugs that may affect platelet function. Specific deferral time periods should be determined by expert committees with broad scientific input.

This Draft Guidance states that if a collection site cannot perform a pre-donation platelet count, a platelet count specified by the device manufacture or a post-donation count from a previous collection should be used to set the target platelet yield (page 5, Section III B). What is the rationale behind using a previous post-donation platelet count to collect a current donation? On review of our collection data for the last 18 months, there were approximately 1,922 first-time apheresis platelet donors (where no pre-donation platelet count was available) and less than 1% of these donors had pre collection platelet counts of 149,000/uL or lower (determined post collection). Upon review of these donors' subsequent pre-donation platelet counts, no adverse events were noted. As previously stated, we are of the opinion that post-collection samples would give a falsely low platelet count and not reflect the donor's true platelet count. If a post-donation platelet count is used to determine target yields, it may result in either inappropriate ineligibility of the donor or the donor spending more time than necessary on the equipment.

Recommendation: Delete the use of a previous post-donation platelet count to set the target platelet yield. Allow collection facilities to decide whether to use a default platelet count or some combination of the donor's previous pre-donation platelet counts.

The Draft Guidance states that "You should collect only a single Platelets, Pheresis collection from first-time donors who do not have a pre-donation platelet count" (Page 5, Section III B 1). Collection of a single apheresis platelet is based on several factors (i.e. donor's height, weight, and default platelet count used by the facility) and while a single collection can be targeted, it cannot be guaranteed. For most, if not all collection facilities, this would be a manual process as computer systems would not be able to control this.

Recommendation: Delete the requirement for single platelet collections from first time donors where platelet count is not known.

This Draft Guidance states that a maximum of 24 Platelet, Pheresis products should be collected from a donor in a 12 month period (page 6, Section III B, 2). We know of no data that supports the collection of 24 products/year versus the current 24 collections/year. This will negatively impact platelet product availability and make the blood supply less safe by relying on whole blood derived platelets, exposing patients to a greater number of donors and using an inferior bacterial detection methodology such as pH dipstick. The reference sited in the draft by Lazarus et al, (ref 21) concludes that clinically significant thrombocytopenia (in regular plateletpheresis donors) is unusual when robust, continuous review and appropriate deferral policies are implemented. These

controls are in place based on existing guidance and standards. In addition, this would require manually tracking as our computer system would not be able to control the donation interval by number of products donated. We believe and all evidence suggests that platelet apheresis with the current 24 collections per year is a safe process. We do not see how these changes will increase donor safety.

Recommendation: Retain the current guidelines for frequency of platelet apheresis procedures in a donor.

This Draft Guidance states that a post-donation platelet count should be performed after each collection (page 6, Section III B, 2). There was no time frame and no rationale given for performing the post-donation platelet count. The primary donor safety issue is that donors not undergo platelet pheresis with a platelet count of <150,000/uL. We do not see how this change will increase donor safety.

Recommendation: Delete specific post-donation testing requirements

This Draft Guidance states a maximum total volume for all products associated with each platelet collection (page 7, Section III B, 4). This is not consistent with AABB Standard 5.5.4.1 (23rd ed.) which states that the combined volume of red cells and plasma removed from the donor shall follow criteria for the FDA-cleared device used. There are several FDA-cleared devices where the allowable volume of the product is < 15% of donor's total blood volume. We do not see how this change would benefit the donor or the product.

Recommendation: Blood loss should be based on donor blood volume and not associated with the product

This Draft Guidance states that the physician must certify in writing that the donor's health permits the collection of platelets for dedicated donations (page 7, Section III, C). Clarification is needed here. Does this mean for each donation or for each donor? As we have a process in place that controls restricted donations and requires physician involvement at appropriate times, we see no value in a physician signature before each donation.

This Draft Guidance states that a qualified physician be able to arrive at the premises within 15 minutes (page 7, Section III D). This would drastically reduce the number of apheresis platelets that could be collected. Donors are currently cared for in a highly acceptable manner that includes access to emergency care. We see no value in having a physician trained in pathology, blood banking or hematology be on site or within 15 minutes during apheresis collections. Our physician on-call (24/7) is able to direct staff in the event of an emergency.

Recommendation: Delete this requirement. We will follow our existing emergency response plans.

Section VI: Process Validation

The Draft Guidance states that for validation, both residual WBC count (if leukocyte reduced) and percent recovery should be performed (Page 10, Section VI B). Percent recovery is not applicable for non-filtration methods of leukoreduction.

Recommendation: Clarify that percent recovery performance qualification is required for leukoreduction by filtration only.

The Draft Guidance describes several criteria for performance qualification for validation which in our opinion appear excessive or need further clarification (Page 11, Section VI D).

The guidance states "...a minimum of 60 consecutive single (30 for double and 20 for triple) collections for each type of automated blood cell separator..." should be tested. The total number of collections that would need to be tested is unclear. Is the number of collections intended to be 60 singles, plus 30 doubles, plus 20 triples or a combination of 60 products? If the former, we believe your recommended validation approach would be excessive and very difficult to complete in a timely manner. In addition, the paragraph further states "product performance qualification should be completed for each automated blood cell separator in your establishment". Again, clarification is requested on whether the term "automated blood cell separator" refers to each specific machine utilized by the blood collection facility or specific manufacturer (i.e. Amicus vs. Trima) used. This clarification is also needed for QC monitoring (Page 19, Section VII C 2). If the intent is for a blood establishment to test 60 consecutive single collections, 30 double and 20 triple collections on <u>each</u> cell separator instrument, this is extremely excessive.

Recommendation: Clarify the total number of collections per type of automated collection device for validation. Performance qualification and QC monitoring should be determined on each manufacturer used at a blood collection facility with representative samples from each individual instrument.

The Draft Guidance states "Perform bacterial contamination testing on 500 collections with 0 failures". Since we currently perform quality control testing for bacterial detection on 100% of our apheresis platelet products we are unclear of the intent of this requirement. With nearly 2 years experience of 100% quality control testing for bacterial contamination, this proposed testing would provide no additional value to what is already being performed. In addition, you have made the requirement of "0" failures but no definition of the term "failure" is provided. What is meant by "0 failures"? Zero "initial positive", 0 "true-positive", 0 "false-positive", or 0 "false-negative"?

Recommendation: Specify the performance qualification for bacterial contamination to reflect the current industry contamination rate standard and clarify what is meant by "O failures".

The Guidance states that performance qualification testing should be performed throughout the shelf-life of the product, i.e. test one third of the products during the first third of the dating period; one third during the second third of the dating period, and one third the day of outdate (Page 11, Section VI D). Performance of the testing in this manner would be logistically difficult to meet. In actuality, if 100% of the products pass qualification testing at time of outdate or issue, testing the products throughout the dating

period seems unnecessary as different storage times will be reflected through natural variation of product issue.

Recommendation: Such detailed testing requirements for qualification throughout the 5-day dating period should be deleted from the Guidance. Recommend that a representative sample be tested on day of outdate.

Section VII. Quality Assurance (QC) and Monitoring

The Guidance states that the Medical Director should be notified when a donor has a post collection platelet count less than 100,000/uL, and a donor should be deferred until his/her platelet count has returned to at least 150,000/uL. (Page 17, Section VII B 1) This recommendation needs a number of clarifications. Although, we agree that any time a donor has a platelet count of 100,000/uL or less the Medical Director be notified (and is at our facility with further follow-up and testing, if appropriate), this requirement infers that it be based on a post-collection platelet count. We believe that a blood sample obtained post collection for a platelet count is unnecessary and provides no added safety for the donor. In fact, the manufacturers' safety specifications for FDA 510K cleared devices allow for platelet counts of 100,000/ul or 80,000/uL at the end of collection. This requirement would seem to contradict an approved medical device labeling. We believe that the key requirement is that donors not undergo plateletpheresis if their pre-donation platelet count is less than 150,000/uL.

Additionally, the Guidance recommends that the donor's records be reviewed before each donation to monitor the donor's ability to recover his/her baseline platelet count. (Page 17, Section VII B 1) We agree that the donors' records be reviewed on a periodic basis

but believe that the requirement for review prior to each donation is unreasonable. In addition, reviewing donor's records prior to each donation when the donation interval is 8 weeks or greater seems excessive.

Recommendation: Delete the specific platelet count limit at which medical directors should be notified and delete the specific requirement that donor's records be reviewed "prior to each donation". In lieu, recommend that each collection facility have an established process for notification of medical director and review of donors' records.

The Draft Guidance recommends that before a subsequent donation from a donor who has reported an adverse reaction, including red blood cell losses in the previous 8 weeks, total volume loss, and low donor platelet counts, that a qualified physician or designee reviews the records of the adverse reaction report and subsequent investigation. (Page 17, Section VII B 2) The requirement appears to be inclusive of all adverse events, whether major or minor. We strongly disagree and are of the opinion that minor reactions (i.e. hematomas or simple vasovagal reactions) or red blood cell losses do not require a review of the report and/or investigation by a physician prior to subsequent donation.

Recommendation: Restrict the requirement to severe donor reactions that require medical intervention and/or hospitalization.

The Guidance establishes that absolute red cell loss must be determined per collection and donor eligibility be based on red cell loss as stated in Table 2 (Page 17, Section VII B 3). In this table, the second donor eligibility criteria (i.e. donor not eligible to donate for

8 weeks from 2nd RBC loss) would be difficult to track via our current computerized system. A manual process would need to be implemented which would be prone for error. Most computerized systems currently track RBC loss per collection and base eligibility on annual RBC loss not RBC loss per 8 weeks. In order to comply with this requirement computer software would need to be redesigned. In addition, if on subsequent donations after a donor has had an RBC loss of <200 ml, the donor has an acceptable hematocrit (≥38%), this eligibility requirement appears too restrictive and does not add to donor safety.

Recommendation: Delete 2nd eligibility criteria in Table 2.

The Draft Guidance states that residual WBC counts be obtained on all collections that do not utilize an automated leukocyte reduction technology (Page 19, Section C). The Haemonetics MCS+ LN9000 apheresis platelet machine uses an in-process filtration technique for leukoreduction. Requiring 100% residual WBC counts on products from this technology is unduly burdensome as acceptable WBC counts were demonstrated in both validation and monthly QC. Since implementing this technology in February of 2004, our QC failures for the MCS+LN9000 products have been similar to those for our products collected by automated leukocyte reduction technology (0.31% versus 0.24%).

Recommendation: Delete the requirement for residual WBC counts on all collections that do not utilize an automated leukocyte reduction methodology.